NTP
National Toxicology Program

Update on NTP Studies of Dietary Supplements/Herbal Medicines

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Overview

- Introduction to dietary supplements
- How to approach the study of dietary supplements
- Update on NTP studies
- Future directions and interagency coordination

Dietary Supplements and DSHEA

- Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994.
- A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet.
  - vitamins, minerals, herbs or other botanicals, amino acids, and a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract or combinations of these ingredients
  - intended for ingestion in pill, capsule, tablet or liquid form
- Not for use as a conventional food or as the sole item of a meal or diet
- Must be labeled as a “dietary supplement”

Use of Dietary Supplements

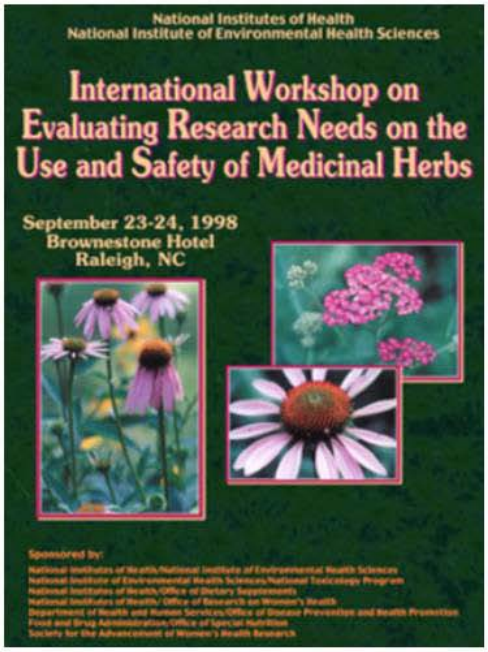
- Nutrition Business Journal (NBJ) estimates
  - Total sales of all dietary supplements
    - 2006 at $22.1 billion
  - U.S. herbal dietary supplement sales
    - 2006 at $4.59 billion
    - 2007 at $4.79 billion

National Health Interview Survey (NHIS)/CDC

- Complementary and Alternative Medicine (CAM) Use
  - Barnes et al 2008
- Cross-sectional household interview survey of the U.S. civilian non-institutionalized population. (30,000 families)
- One in nine children and four in ten adults used CAM therapy
  - Most commonly used nonvitamin, nonmineral, natural products
    - fish oil or omega 3 or docosohexaenoic acid (DHA), glucosamine, echinacea, flaxseed oil or pills, ginseng and combination herb products
- More than one-half of these products were for "wellness"
  - Not used to treat or prevent the child's specific conditions
  - Suggest possible long term use

NTP Workshop 1998

- Recommendations from the workshop:
  - Research on potential toxicity associated with high dose or prolonged use
  - Identification and standardization of product ingredients by industry
  - Increased consumer education through package inserts
  - Identification of herb-drug and herb-herb interactions
  - Research on risk to sensitive subpopulations
- Mathews et al (1999)
  - EHP 107:773



Special Considerations Compared to Other Test Articles

- Which product should be studied
  - Different plant species/plant parts
  - Multiple formulations
- Are all sources the same
  - Possible variations due to growing and harvesting conditions
  - Possible variations due to processing
- Characterization issues
  - Materials have different physical and chemical characteristics
  - Analytical techniques are selective
  - Characterization must fit test article and study requirements

Three lots of Black Cohosh root powders

General Approach

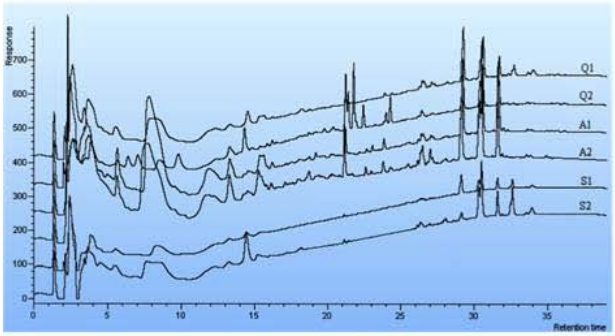
- Known Actives
  - identified from the literature
  - authentic standards when available
  - common classes
- Fingerprinting – complex pattern for comparison
- Detected components should be identified whenever possible
- Mass Spectrometry – to evaluate the presence of undetected actives discovered after bioassay is complete
- Impact on nutritional status – vitamins, metals, amino acids, fatty acids

Efforts at Total Composition

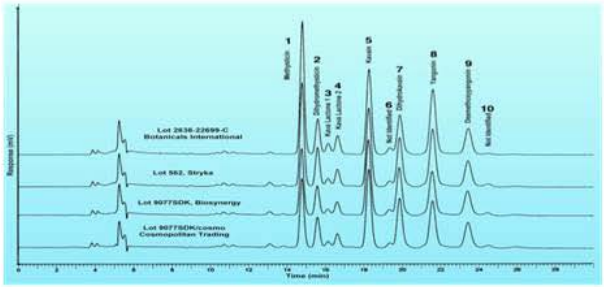
- Nutritional Analysis
  - Protein, Moisture, Fat, Ash, Fiber
  - Vitamins A, E, B12, Thiamin, Biotin, Folic Acid, Riboflavin, Niacin, Pantothenic Acid, Choline, Pyridoxine hydrochloride
  - Fatty Acids
  - Amino Acids
- Contaminants
  - Metals
  - Pesticides
  - Mold Toxins

Lot to Lot Variability

- In some cases high
  - E.g. Echinacea



- In some cases low
  - E.g. Kava kava



NTP Areas of Emphasis: Dietary Supplements and Herbals

- Multipurpose
  - Aloe vera, Echinacea, gum guggul, kava, milk thistle, pulegone/pennyroyal, and senna laxative
- Women's health
  - Black cohosh, gum guggul, dong quai,
- Cancer chemopreventatives
  - Green tea extract, indole carbinol, milk-thistle extract, resveratrol, melatonin
- Anti-aging/wellness
  - Ginseng, glucosamine/chondroitin sulfate, Ginko biloba, vincamine
- Weight loss/sports aids
  - Usnea lichen/usnic acid, chitosan, Garcinia cambogia, bitter orange extract, androstenedione

Rationale for Selection

- Size of the population using a given DS
  - High NBJ sales figures
  - Surrogate for exposure
- Use pattern
  - Long term use as a chemotherapeutic or for wellness
  - Use by children and women of child bearing age
- Biological activity
  - Based on suggested use
  - Based on constituent profile

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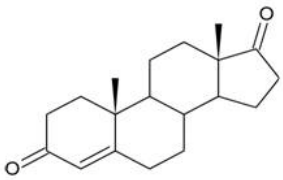
2009-NTP Technical Reports



- Androstenedione
  - Concern over consumer abuse by body builders
- Goldenseal Root Powder
  - Used by consumer for infections. Lack of information on safety

- Ginseng
  - Study based on its widespread use and lack of toxicity information.
- Milk Thistle extract
  - Popular supplement thought to have beneficial effects on the liver

- Pulegone
  - Used as flavoring agent, fragrance and herbal medicine

Future Technical Reports

- Chronic studies-
  - Aloe Vera
  - Alpha/beta thujone mixture
  - Kava kava
  - Green tea extract
  - Ginkgo biloba
  - Indole-3 carbinol
- Genetically modified models
  - Senna -p53 model

New NTP Research Concepts 2009

- February 2009
  - Dong Quai
- December 2009
  - Butterbur
  - Evening Primrose Oil
  - Valerian

Impact and Utility

- Use of NTP data by FDA in decision-making
  - Comfrey, ephedra
- Increased coordination with FDA
  - Several meetings with with FDA/CFSAN and NIEHS staff
- Establishment of interagency coordination group
  - NIEHS/NTP, NIH-ODS, FDA/CFSAN, FDA/NCTR
  - Prioritization of agents for study
  - Nominations of high priority from members to NTP
  - Identification of effects and potentially influential data
  - Design and conduct of additional studies to expand mechanistic and translational understanding

Future Directions

- Chemical and biologically based screening and prioritization
  - Short term *in vivo* assays
  - High-density *in vitro* assays
- Provide context on data from NTP studies
  - Representativeness of test article to other formulations
  - Exposure extrapolation
  - Mode of action studies
- Human studies
  - Discussions with NIEHS Clinical Research Unit

Summary

- Use of DS is widespread
- Experience in handling complex "testing" issues
- Current and future major area of emphasis for the NTP
- Increasing coordination to ensure NTP obtains the most needed information to inform public health decision-making.